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Review

Food additives and genotoxicity

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Abstract

In today's changing conditions, there has been an increase in the consumption of ready-made food with the change in eating habits. Moreover, parallel to the increase in ready-made food production, there has been an increase in the food additives used. The dose amounts of food additives are determined as a result of experimental analyses. However, some additives show long-term toxic effects on the human body in genotoxicity tests. In this review, definition of substances, purposes of usage, classification, genotoxicity, definitions of tests and publications of genotoxicity studies in food additives were discussed. The search was conducted in peer-reviewed journals using Science-Direct, Web of Science and Google Scholar. In this study, genotoxicity studies conducted with food additives between 2015-2021 were complied. For this purpose, the keywords ‘‘food additive’’, ‘‘genotoxicity’’ were used together and research articles were included in this study.

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1. Introduction

It has become inevitable that food items have been changed with the development of technology. Businesses have increased the production of ready-made foods and also food additives according to people's demand for snacks and more practical foods. Shelf life and preserving properties are important parameters for using food additives. However, excessive consumption of ready-made foods and also additives cause carcinogenic and mutagenic effects on human body (Ayaz and Yurttagül, 2012).

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1.1. Food Additives

The preference for additives in the food market has emerged from the diversity of the consumers' taste and therefore different production methods brought by the development of technology. Current production techniques such as increase in yield, minimising losses, increasing product quality, standardisation and the shelf life of products and producing new foods with different formulas have been commonly used in food industry. The definiton of food additive is "not consumed as a food on its own but a characteristic component of the food with or without nutritive value" according to Turkish Food Codex and Regulation on Food Additives. These are substances that are expected to be a preferred food componentin itself or its by-products as a result of its packaging, addition to food at transport or storage levels (Ayper and Binokay, 2010).

The classification of food additives according to their main functions can be summarized as follows colourants, preservatives, sweeteners, antioxidants, emulsifiers and acid-base providers.

Colourants: It is a class of food additives that can correct the colour without affecting the taste of the food (EFSA, 2018; Brancato et al., 2018).

Preservatives: It is the preferred class with the function of preventing the spoilage of food, ensuring the safety of food by keeping the long shelf life and preventing microorganisms production.

Sweeteners: It is used to improve the taste of foods and remove the irritating odours at the level of food production.

Antioxidants: They are preferred to delay or prevent colour loss related to undesirable odours, aromas, flavour changes, enzymatic darkening, to prevent or delay the bitter taste that occurs in fatty foods.

Emulsifiers: They provide uniform mixing of the fat and water-soluble substances in the food.

Acid-base providers: They are preferred to control and regulate the pH level of the food at different stages during production and also the final product (EFSA 2018; Brancato et al., 2018).

1.2. EFSA (The European Food Safety Authority)

EFSA is the international organisation that guarantees the food safety of the European Union since 2002. This organisation evaluates the risks in the food chain scientifically and therefore help guarantee safe food in the European continent. The Food Safety Authority's work covers all areas involving the food chain: nutrition, food and feed safety, animal health and welfare, phytosanitary and plant protection. EFSA provides independent high-quality scientific advice and evaluation based on up-to-date scientific data to the European Commission, the European Parliament and European Union (EU) decision-makers such as Member States. Thus, it helps risk managers in Europe, making informed decisions to improve EU food safety. By working closely with partners and stakeholders, EFSA contributes to a high level of consumer protection while ensuring the reliability of EU food sources (Erkmen, 2010).

1.3. Effects of Food Additives on Health

It has been observed that non-food chemicals have negative effects on human health. Numerous studies have found that consuming excessive amounts of synthetic food additives can cause gastrointestinal, respiratory, dermatological and neurological reactions (Chassaing et al., 2015). In some studies, it has also been observed that emulsifiers and sweeteners change the composition of the intestinal microbiota and facilitate the translocation of bacteria in intestinal epithelium. It is thought that the consumption of food additives such as carboxymethylcellulose or polysorbate 80 significantly reduces the thickness of the mucus layer and has a role in inflammatory bowel diseases such as ulcerative colitis and Chron's disease as well as colon cancer, obesity and diabetes (Cowan et al., 2013; Tayfur, 2014). It prevents the growth of *Clostridium botulinum* which is a harmful bacteria that develops in meat and meat products and prevents high toxicity to the consumer. *Clostridium botulinum* is the most important bacterium with a highly toxic effect on humans and animals (Skypala et al., 2015). Nitrite passes into the blood and combines with haemoglobin to form methemoglobin. Methemoglobin inhibits the oxygen-carrying function of haemoglobin.

Nitrites and nitrates can turn into cancer-causing components such as nitrosamines and become active in many organs such as liver, respiratory system, kidney, urinary bladder, pancreas, stomach and cause cancer (Chassaing et al., 2015). Natural food ingredients and added food additives may cause allergic reactions depending on the dose taken and the individual's particular sensitivity. Clinical symptoms after ingestion of food additives are angioedema or chronic urticaria. However, symptoms may also include severe anaphylactoid or anaphylactic reactions such as atopic dermatitis, flushing, abdominal pain, diarrhoea, hypotension, and asthmatic reactions (Stevens, 2013). Food colourants are thought to release prostaglandins and histamine in urticaria with a direct pharmacological effect in sensitive individuals rather than an allergic reaction. It has been reported that colourants also cause behavioural disorders such as hyperactivity, especially in children aged 3-9 years (JECFA, 2013).

1.4. Genotoxicity Tests

Standard *in vitro* and *in vivo* mutagenicity tests can provide a link between the carcinogenic and mutagenic effects of the genetic system and the substances. There are different genetic toxicity tests and some of them are discussed below.

The Ames (Salmonella/Microsome Mutagenicity) assay is a short-term and frequently applied test for detecting mutations at the gene level and preferred as a genotoxicity assay (Zeiger, 2019). The Ames assay is based on the effect of a mutation that confers the ability to synthesise histidine to strains with mutations that have lost their ability to synthesise histidine. Because the chemical component is estimated to have a mutagenic effect, it provides clear information about the genotoxicity level (Omurtag et al., 2013).

Comet assay is an easy, fast and reliable sensitive genotoxicity test applied to calculate the damage and level of DNA (Azqueta and Collins, 2013). The method of the comet assay is that the negatively charged DNA fragments in the nucleus generally isolated from living tissues are fixed into the thin agarose gel and the protocol is applied in the electrophoretic environment. If there is a break in the chain of single or double-stranded DNA, the broken one has a different molecular weight and electrical charge. It is based on the principle that fragile DNA molecules migrate at a variable rate in the electrophoretic field. It can be applied

in different types of cells and DNA breaks formed in the cell can be determined visually and create a comet appearance (Güner and Muranlı, 2013).

Sister Chromatid Exchange assay is expressed as the symmetrical exchange of DNA replica products between homologous locus of sister chromatids. Double-stranded DNA breaks are repaired by the general recombination method. Bromodeoxyuridine acts like a thymine analogue in DNA is added to the cell culture to make DNA breaks visible. During the cell cycle, bromodeoxyuridine passes between sister chromatids and mutual exchange of DNA fragments in homologous chromosomes is observed. Staining difference causes sister chromatids to stain differently from each other and thedifferences between sister chromatids in DNA are detected (Sezginer and Feruzan, 2016).

Micronucleus is generally formed from deficiencies in gene that controls the cell cycle and errors in the mitotic spindle. It arises from its different parts in the kinetochore or mitotic apparatus and chromosomal damage. It occurs during the mitosis division of the cell and not included in the main nucleus. Whole chromosomes are formations consisting of acentric chromosome fragments (Hayashi, 2016).

Chromosomal aberrations assay occurs as a result of damage to the level of DNA. Chromosome breaks are caused by unrepaired double-strand breaks in DNA while chromosomes with new structures are caused by incorrect repair of chain breaks in DNA. High chromosome abnormalities frequencyoccurs when such damages in the genetic material can not be repaired, indicating an increased cancer risk (Şekeroğlu and Atlı, 2011). The chromosome aberrations assay is a standard method frequently used for the detection of various structural and numerical chromosomal abnormalities induced by mutagens. Chromosomal abnormality frequency can be evaluated in mammalian cell cultures by *in vitro* chromosome aberrations assay and bone marrow cells. In addition, *in vivo* chromosome aberrations assay also allows the evaluation of factors such as metabolism, pharmacokinetics and DNA repair mechanisms which may vary depending on the species and tissue, especially in the determination of mutagenic damage (Şekeroğlu and Atlı, 2011).

1.5. Some of the Genotoxicity Studies with Food Additives

Food additives are substances that directly or indirectly contribute to human nutrition. For this reason, studies on genotoxic effects along with its effects on health are quite abundant. Among these studies, those carried out between 2015-2021 were summarised (Table 1). One of these studies is related to the genotoxic effects of monopotassium glutamate, calcium diglutamate, monoammonium glutamate and magnesium glutamate in root tip cells of *Allium cepa* (Türkoğlu, 2015). Different concentrations of the mentioned food additives were applied at different times. All concentrations of these chemicals have been reported to exert an inhibitory effect on cell division in root tips of *Allium cepa* and cause a decrease in the mitotic index. Micronucleus assay and comet assay techniques were used. In addition, these compounds have been reported to increase the frequency of chromosomal aberrations in the assay material (Türkoğlu, 2015). In another study conducted in 2016, *in vitro* genotoxic effects of monosodium glutamate on human peripheral lymphocytes were determined by a chromosomal aberrations, sister chromatid exchange, micronucleus, comet assay. It was observed that monosodium glutamate significantly increased chromosomal aberrations, sister chromatid exchange and micronucleus frequency compared to control. According to the comet assay results, tail density, tail length and tail moment also increased significantly when compared to the control. It has been reported that obtaining results indicated that monosodium glutamate has a genotoxic effect on human lymphocytes (Ataseven et al., 2016). Allura Red is used as a food color additive. *In vivo* micronucleus assay (bone marrow) and comet assay (liver, stomach, and colon) were performed using male young adult mices. As a result, it was determined that Allura Red did not have genotoxic activity in both assays (Bastaki et al., 2017). In a study conducted in 2017, the genotoxic effects of potassium propionate (E283), a food preservative, were investigated. *In vitro* micronucleus assay technique was used in human peripheral blood lymphocytes. According to the test results, micronucleus frequency was increased as a result of potassium propionate treatment (Ataseven et al., 2017). Sodium benzoate and potassium sorbate are widely used today. Genotoxic potential of their mixture was investigated by micronucleus assay in human peripheral blood lymphocytes *in vitro*. As a result, it was observed that the mixture could have a genotoxic effect (Mamur et al., 2018). In a different study, the genotoxic effects of sunset yellow were investigated. Human peripheral lymphocyte cultures were studied with chromosomal aberrations assay and micronucleus assay. As a result of this study, it was determined that sunset yellow were showed dose-dependent genotoxic potential in both assays (Haverić et al., 2018). Due to the widespread use

of stevia extracts, it was investigated in human peripheral blood lymphocytes. Chromosomal aberrations assay and micronucleus assay were used. No genotoxic effects were observed in either assay (Uçar et al., 2018). With the development of the food industry, the use of potassium nitrate has become widespread. Somatic mutation and recombination test (SMART) and comet assay techniques were used. *In vivo* experiments were performed in the animal model of *Drosophila melanogaster*. Both assays showed a tendency to high levels of genotoxic potential of potassium nitrate (Aledwany et al., 2018). In an another investigation conducted in 2018, genotoxicity and cytotoxicity of sodium acetate on Human Umbilical Vein Endothelial Cells (HUVEC) were determnined. Cytotoxicity was investigated by MTT assay and genotoxicity was investigated by DNA fragmentation. In conclusion, sodium acetate did not show cytotoxic and genotoxic effects in this study (Mohammadzadeh-Aghdash et al., 2018). Aspartame is one of the most preferred sweeteners today. It was evaluated by Ames assay and *in vivo* micronucleus assay. As a result, no genotoxic or mutagenic potential was observed in either test (Otabe et al., 2019). The genotoxic effects of ascorbic acid, benzoic acid, citric acid and sorbic acid in human peripheral blood lymphocytes were investigated using *in vitro* micronucleus assay. It was concluded that high concentration of benzoic acid, citric acid and sorbic acid were shown cytotoxic and genotoxic effect (Bogar and Tuylu, 2019). Methanyl yellow and carmoicine are widely used two azo dyes. There is a lot of controversy about these two dyes. To evaluate the genotoxicity of these food dyes, *Allium cepa* test was performed and mitotic index and chromosomal aberrations were examined. It was determined that methanol yellow and carmoicine had a significant decrease in the mitotic index. In addition, it was determined that different kinds of chromosomal aberrations were induced, especially at high concentrations. For this reason, it was emphasized that these two food additives should be used in limited doses (Khan et al., 2020). In different investigation, *in vitro* genotoxic effects of monopotassium glutamate (MPG) and magnesium diglutamate (MDG) were studied in human peripheral blood lymphocytes. Chromosomal aberrations assay were studied with sister chromatid exchange, micronucleus assay and comet assay. In these four tests, clastogenic, mutagenic and cytotoxic effects were detected in human peripheral lymphocytes *in vitro* (Avuloğlu-Yılmaz et al., 2020). In another study in 2020, the genotoxicity and cytotoxicity effects of glycerol triacetate (E1518) were investigated. Mitotic index and chromosomal aberrations assay were used in *Allium cepa* root tip cells. As a result, cytotoxic and genotoxic effects of E1518 were observed (Kaya, 2020).

Titanium dioxide (E171) is considered an inert and indigestible substance. It is also used in food packaging, pharmaceutical and cosmetic fields. Biological effects of E171 on germination percentage, root elongation, mitotic index, comet assay and micronucleus were observed in *Lens culinaris* and *Allium cepa*. As a result, it detected dose-related genotoxicity (Bellani et al., 2020). Silver food additive (E174) has recently increased its use in many consumer products, including cosmetics and food packaging. The genotoxic effects of E 174 were analysed using comet (mouse liver, blood, spleen, duodenum and kidney tissues) and micronucleus (mouse spleen lymphocytes) assays. In all tissues tested, no genotoxic or tissue damage was detected in either assay (Narciso et al., 2020). The genotoxic effects of sodium sulfite, boric acid and benzoic acid, which are frequently used in daily meals, were investigated. The genotoxic effect of these three food preservatives was investigated in *Drosophila melanogaster* by SMART and comet assay. All three food additives caused increased tumor induction and frequency in the SMART, and also induced DNA damage in the comet assay (El-Hefny et al., 2021). Potassium sorbate is used as a food preservative. The genotoxic (with chromosomal aberrations and micronucleus assays) and cytotoxic (with MTT test) effects of potassium sorbate and its ability to induce oxidative stress (with superoxide dismutase activity) in human lymphocytes were investigated. As a result, it was determined that potassium sorbate induced cytotoxic and genotoxic effects in human cells and caused oxidative stress (Pongsavee and Mishra, 2021). Flavoring food additives have an important area in the food industry. Merismatic stem cells of *Allium cepa* L. were preferred in order to evaluate the toxicity of the aroma synthetic chocolate additive. As a result, the aroma of chocolate caused cytotoxic, genotoxic and mutagenic effects on root meristems (Frâncica et al., 2021).

Table 1. Genotoxic effects and results of food additives

Food Additivies	Research / Result	References
-Monopotassium Glutamate -Calsium Diglutamate -Monoammonium Glutamate -Magnesium Glutamate	CA / Mitotic Index / MN (*Allium cepa*) + / + / +	Türkoğlu, 2015
-Monosodium Glutamate	CA / MN / SCE In human peripheral lymphocytes + / +/ +	Ataseven et al., 2016
-Allura Red	Comet assay / MN *In vivo* - / -	Bastaki et al., 2017
-Potassium Propionate	MN In human peripheral lymphocytes +	Ataseven et al., 2017
-Sodium Benzoate -Potassium Sorbate	MN In human peripheral lymphocytes +	Mamur et al., 2018
-Sunset Yellow	CA / MN In human peripheral lymphocytes + / +	Haverić et al., 2018
-Stevia Extracts	CA / MN In human peripheral lymphocytes - / -	Uçar et al., 2018
-Potassium Nitrate	SMART / Comet assay Drosophila Melanogaster system + / +	Aledwany et al., 2018
-Sodium Acetate	DNA Fragmentation / MTT Human Umbilical Vein Endothelial Cells(HUVEC) - / -	Mohammadzadeh-Aghdash et al., 2018
-Aspartame	Ames assay / MN *In vivo* - / -	Otabe et al., 2019
-Ascorbic Acid -Benzoic Acid -Citric Acid -Sorbic Acid	MN In human peripheral lymphocytes +	Bogar and Tuylu, 2019
-Methanyl Yellow -Carmoisine	Mitotic Index / CA *Allium cepa* + / +	Khan et al., 2020
-Monopotassium Glutamate -Magnesium Diglutamate	CA / Comet assay / MN / SCE In human peripheral lymphocytes + / + / + / +	Avuloğlu-Yılmaz et al., 2020
-Glycerol Triacetate	CA / Mitotic Index *Allium cepa* root tip cells + / +	Kaya, 2020
-Titanium Dioxide	CA / Mitotic Index / MN *Allium cepa* and *Lens culinaris* + / + / +	Bellani et al., 2020
-Silver	Comet assay / MN *In vivo* - / -	Narciso et al., 2020
-Sodium Sulfite -Boric Acid -Benzoic Acid	Comet assay / SMART Drosophila Melanogaster System + / +	El-Hefny et al., 2021
-Potassium Sorbate	CA / MN İn rat and hamster cells, in human peripheral lymphocytes + / +	Pongsavee and Mishra, 2021
-Flavor Synthetic Chocolate Additive	Mitotic Index Meristematic root cells of *Allium cepa L.* +	Frâncica et al., 2021

*CA, Choromosomal Aberrations Assay; MN, Micronucleus Assay; SMART, Somatic Mutation and Recombination Test; +, Positive genotoxic results; -, Negative genotoxic results.

2. Conclusion

The rapid increase in the world population, environmental pollution, economic imbalance and lack of education negatively affect food problems. This makes it difficult to obtain safe food. Considering the effects of food additives as a whole, most of the commonly used food additives were found to be genotoxic. The purpose of testing the genetic toxicity of ingredients in food additives and other foods are to minimise the health risk to consumers. Genetic damage to somatic or germ cells is associated with harmful health effects such as cancer, hereditary diseases, and degenerative disease states. Even if the food additives that are frequently used in foods are used in amounts that do not harm health, it should be taken into account that food additives may accumulate in the body over time and may be harmful, thus threatening human health directly or indirectly. Therefore, care must be taken in their use and existing rules should be followed.

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